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AF/1641

TRANSMITTAL OF APPEAL BRIEF (Small Entity)

Docket No.
MSU 4.1-587

In Re Application Of: **Evangelyn C. Alocilja and Zarini Muhammad-Tahir**

Application No.	Filing Date	Examiner	Customer No.	Group Art Unit	Confirmation No.
10/074,499	February 13, 2002	Leon Y. Lum	21036	1641	4246

Invention: **CONDUCTIMETRIC BIOSENSOR DEVICE, METHOD AND SYSTEM**

COMMISSIONER FOR PATENTS:

Transmitted herewith is the Appeal Brief in this application, with respect to the Notice of Appeal filed on:

November 28, 2007

☒ Applicant claims small entity status. See 37 CFR 1.27

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Dated: **January 22, 2008**

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I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)] on January 22, 2008 .

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 10/074,499	Confirmation No. 4246
Applicants	: Evangelyn C. Alocilja and Zarini Muhammad-Tahir	
Filed	: February 13, 2002	
TC/A.U.	: 1641	
Title	: CONDUCTIMETRIC BIOSENSOR DEVICE, METHOD AND SYSTEM	
Examiner	: Leon Y. Lum	
Docket No.	: MSU 4.1-587	
Customer No.	: 21036	

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
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Alexandria, VA 22313-1450

BRIEF UNDER 37 C.F.R. § 41.37

Sir:

This is an appeal from a final rejection in the above entitled application. The claims on appeal are set forth as Claims Appendix. An oral hearing will be requested. Enclosed is the fee due upon filing of the Brief.

(1) REAL PARTY IN INTEREST

The real party in interest is the Board of Trustees of Michigan State University, East Lansing, Michigan, a constitutional corporation of the State of Michigan, which is the assignee of the above entitled application.

(2) RELATED APPEALS AND INTERFERENCES

There are no pending related appeals and interferences.

(3) STATUS OF CLAIMS

Claims 1-3, 7-10, 14-16, 18, 19, 21, 22, 24 and 26 are pending in the application. Claims 1-3, 7-10, 14-16, 18, 19, 21, 22, 24 and 26 were rejected. Claims 4-6, 11-13, 17, 20, 23 and 25 were subject to a Restriction Requirement and were canceled in the prosecution. No claims have been allowed.

(4) STATUS OF AMENDMENTS

No Amendments were filed after the final rejection dated September 4, 2007.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter in Claim 1 is a biosensor device (support for this claim is found at page 3, line 16 through page 4, line 6 of the specification; illustrated in Figures 1A-1E) which comprises:

a strip of a substrate (page 10, lines 2-4 of the specification) having at least two zones (page 10, lines 5-7 of the specification) wherein a

(1) first of the zones contains a first capture reagent (page 9, lines 4-11 of the specification) bound to the substrate in a defined area between electrodes on different sides of the defined area for providing an electrical bias to the defined area; and

(2) a second of the zones containing a fluid transfer medium for supplying a fluid to the first zone, wherein the second zone comprises a second defined area containing a second capture reagent bound to an electrically conductive polymer (page 9, line 12 through page 10, line 1

of the specification), wherein when a fluid sample containing an analyte is bound by the second capture reagent to form a complex (page 10, lines 8-9 of the specification) in absence of electrically conductive metal particles in the complex, the complex migrates to the first zone in the medium and the analyte is bound by the first capture reagent thereby altering a conductivity or resistance of the defined area in the first zone as measured between the electrodes to detect the analyte. The operation of the biosensor device is illustrated in Figures 2A-2C1 as described at page 11, lines 7-18.

The claimed subject matter in Claim 7 is a system for detecting an analyte in a fluid sample (support for this claim is found at page 5, line 7 through page 6, line 4 of the specification) which comprises:

(a) a biosensor device which comprises:

a strip of a substrate (page 10, lines 2-4 of the specification) having at least two zones (page 10, lines 5-7 of the specification) wherein a

(1) first of the zones contains a first capture reagent (page 9, lines 4-11 of the specification) bound to

the substrate in a defined area between electrodes on different sides of the defined area for providing an electrical bias to the defined area; and

(2) a second of the zones containing a fluid transfer medium for supplying a fluid to the first zone, wherein the second zone comprises a second defined area containing a second capture reagent bound to an electrically conductive polymer (page 9, line 12 through page 10, line 1 of the specification) wherein when a fluid sample containing an analyte is bound by the second capture reagent to form a complex (page 10, lines 8-9 of the specification) in absence of any electrically conductive metal particles in the complex, the complex migrates to the first zone in the medium and the analyte is bound by the first capture reagent thereby altering a conductivity or resistance of the defined area in the first zone as measured between the electrodes;

(b) electrical means for supplying an electrical bias between the electrodes; and

(c) measuring means for determining a change in the conductivity or resistance of the first area before and after application of the sample in the second zone to detect the analyte (digital multimeter 19 in Figure 6A as described at

page 18, lines 23-28; and Figure 4 as described at page 19, line 22 through page 20, line 1). The operation of the biosensor device is illustrated in Figures 2A-2C1 as described at page 11, lines 7-18.

The claimed subject matter in Claim 8 is a biosensor device (support for this claim is found at page 6, lines 5-25 of the specification illustrated in Figures 1A-1E) which comprises:

a strip of a substrate (page 10, lines 2-4 of the specification) having at least two zones (page 10, lines 5-7 of the specification) wherein a

(1) first of the zones contains a first antibody (capture reagent of page 9, lines 4-11 of the specification) bound to the substrate in a defined area between electrodes on different sides of the defined area (immobilization of antibody on page 17, lines 3-17) for providing an electrical bias to the defined area; and

(2) a second of the zones containing a fluid transfer medium for supplying a fluid to the first zone, wherein the second zone comprises a second defined area containing a second antibody bound to an electrically conductive polymer (antibody labeling with polyaniline on

page 16, lines 11-20; page 9, line 12 through page 10, line 1 of the specification), wherein when a fluid sample containing an antigen which is bound by the second antibody, bound to the conductive polymer, forms a complex in absence of any electrically conductive metal particles in the complex, the complex migrates to the first zone in the medium and the antigen is bound by the first antibody thereby altering a conductivity or resistance of the defined area in the first zone as measured between the electrodes to detect the antigen (analytical procedure on page 18, lines 6-28).

The claimed subject matter in Claim 14 is a system for detecting an antigen in a fluid sample (support for this claim is found at page 7, line 25 through page 8, line 22 of the specification illustrated in Figures 1A-1E) which comprises:

(a) a biosensor device which comprises:

a strip of a substrate (page 10, lines 2-4 of the specification) having at least two zones (page 10, lines 5-7 of the specification) wherein a

(1) first of the zones contains a first antibody (capture reagent of page 9, lines 4-11 of the specification) bound to the substrate in a defined area between electrodes

on different sides of the defined area (immobilization of antibody on page 17, lines 3-17) for providing an electrical bias to the defined area; and

(2) a second of the zones containing a fluid transfer medium for supplying a fluid to the first zone, wherein the second zone comprises a second defined area containing a second antibody bound to an electrically conductive polymer (antibody labeling with polyaniline on page 16, lines 11-20; page 9, line 12 through page 10, line 1 of the specification), wherein when a fluid sample containing an antigen which is bound by the second antibody, bound to the conductive polymer, forms a complex in absence of any electrically conductive metal particles in the complex, the complex migrates to the first zone in the medium and the antigen is bound by the first antibody thereby altering a conductivity or resistance of the defined area in the first zone as measured between the electrodes (analytical procedure on page 18, lines 6-28);

(b) electrical means for supplying an electrical bias between the electrodes; and

(c) measuring means for determining a change in the conductivity or resistance of the first area before and after

application of the sample in the second zone to detect the antigen (digital multimeter 19 in Figure 6A as described at page 18, lines 23-28; and Figure 4 as described at page 19, line 22 through page 20, line 1).

Claims 22, 24 and 26 related to the use of a multiple array and defined dimensions as disclosed on page 10, lines 21 to 23, page 11, lines 19 to 28 of the specification and in Figures 3 and 4. Claims 4 and 10 are original claims and the language relating to the 1 mm dimension between the electrodes would be incorporated into the specification upon a reversal by the Board.

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

(a) Claims 1-2, 7-9, 14-16, 18-19 and 21 were rejected under 35 U.S.C. §103(a) as being unpatentable over Kim *et al.* (*Biosensors & Bioelectronics* (2000), vol. 14, pp. 907-915).

(b) Claims 3, 10, 22, 24 and 26 were rejected under 35 U.S.C. §103(a) as being unpatentable over Kim et al. (Biosensors & Bioelectronics (2000), vol. 14, pp. 907-915) in view of Roberts et al. (U.S. Patent No. 5,958,791).

(7) ARGUMENT

A. The Examiner rejected Claims 1-2, 7-9, 14-16, 18-19 and 21 under 35 U.S.C. §103(a) as being unpatentable over Kim *et al.* (*Biosensors & Bioelectronics* 2000, 14: 907-915).

Page 5 of the Final Rejection states as follows:

> "Although Kim et al. teach that the preferred embodiment for the second antibody conjugate, which represents a labeling agent, comprises a colloidal gold-antibody conjugate that further includes the electrically conductive polymer on the surface thereof, Kim et al. do teach the "direct labeling" of the antibody with the electrically conductive polymer (see "Conclusions" section on page 914, the first 9 lines). Specifically, Kim et al. state, "This strategy for conductimetric detection could be a better approach that the **direct labeling of the antibody with the** polymer. . .". This would indicate that such a direct labeling between the antibody and the conductive polymer was well known in the art at the time the invention was made. Therefore, it would have been obvious to utilize the "direct labeling" of the antibody with the electrically conductive polymer as disclosed by Kim et al. to achieve the predictable result of altering a conductivity of the measurement area between electrodes. Further, it would have reasonably been held to be within the general skill of a worker in the art to select a known material on the basis of its suitability for the intended use as a matter of obvious design choice. *In re Leshin*, 125 USPQ 416. Additionally, all disclosures of non-preferred embodiments must be considered. *In re Nehrenberg* 126 USPQ 383, *In re Boe* 148 USPQ 507, *In re Lamberti et* al. 192 USPQ 278 (CCPA 1976)".

Page 914 of Kim et al. (5. Conclusions) reads in its entirety as follows:

> "An additional labeling agent comprising a conducting polymer to colloidal gold-antibody conjugates facilitated electric conduction between gold particles captured via antigen-antibody binding. This strategy for conductimetric detection could be a better approach than the direct labeling of the antibody with the polymer by chemical reaction because, <u>in such a case, the protein molecule itself does not contain available sites for electron relay</u>. Therefore, the conductimetric gold tracer could provide a simple procedure for its preparation and also a new concept for quick, sensitive analysis based on immuno-chromatography for a number of clinical indicators, for examples, hormones, protein markers, and infectious organisms. Further enhancement of its performance may be possible by considering at least two additional aspects. First, since the electrodes were screen-printed on the outer surfaces of NC membrane, the surface area for electric connection with the gold tracer that were mostly bound on the inner surfaces of membrane pores could be small. An electrode system providing large contacts can lead to immunosensors with higher sensitivity. Secondly, because the immunoassay is normally carried out at a neutral pH, a conducting polymer label providing the conductivity independent of pH is urged to investigate". (Emphasis Added)

The statement in the Final Rejection is contrary to the teaching of Kim et al. The logic is contrary to the actual statement of Kim et al. The statement teaches away from the invention because of the stated lack of conductivity of the polymer in Kim et al.

The Applicant filed a Declaration Under 37 CFR 1.132 which shows that the polymer is directly linked to the polymer. There is no linker as with the conductive gold particles of Kim et al. This claimed invention is not shown by any of the prior art.

To establish a *prima facie* case of obviousness, basic criteria must be met. There must first be some suggestion or motivation, either in the reference or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. This teaching or suggestion to make the claimed combination must be found in the prior art, not in Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). There is no teaching or suggestion to modify the cited Kim et al. reference so as to provide the claimed biosensor device.

Kim *et al.* discloses a conductimetric membrane strip immunosensor for the detection of human serum albumin (HSA) as an analyte. Kim *et al.* teaches the use of antibodies against the HSA analyte which have been conjugated to colloidal gold particles as a signal generator for the conductimetric immunosensor. Kim *et al.* teaches first to affinity purify antibodies against human serum

albumin (HSA) and then to conjugate the affinity purified antibodies with colloidal gold particles. (Kim *et al.* page 908, last paragraph). The colloidal gold-antibody conjugate is added to a site on the glass fiber membrane before adding an aqueous sample containing the HSA analyte. The sample is absorbed by capillary action into a membrane strip system which is illustrated in Figure 1. The colloidal gold-antibody conjugate binds the analyte to form a complex which travels up the strip to a signal generation pad where an immobilized antibody, also against the HSA analyte, binds the analyte in the complex. The colloidal gold particles captured on the signal generation pad result in a colored signal which can be quantified by optical density values. (Kim *et al.* page 910, second column, last paragraph).

As an alternative to this colorimetric method of detection, " the density of particulate gold, electron-rich metal, can be determined by measuring electric conduction." (Kim *et al.*: page 911, section 3.2, first paragraph). Kim *et al.* teaches placement of two electrodes in the region where the immobilized antibodies bind the analyte in the complex. Since the immobilized antibodies bind the analyte in the complex between the two electrodes, electrical

conductivity was monitored. Kim *et al.* teaches however, that the conductivity signal is "so weak that the maximum signal-to noise ratio was approximately two times lower than the value determined by the photometry. The dose-response curves further revealed that the monitoring based on conductimetry involved a comparatively large variation." (Kim *et al.*: page 911, right column, second paragraph).

Kim *et al.* teaches that with the plain gold particles, poor analytical performances in generating the conductimetric signal "could result from an impaired transfer of electrons along the gold particles spread on the membrane surface." (Kim *et al.* "Discussion", page 913, first paragraph). After conjugating the gold particles to the antibody the "residual surfaces of the gold particles were blocked by adding 0.1 M Tris, pH 7.6, containing 5% casein (1 ml) for 30 min." (Kim *et al.* sentence spanning page 908 and page 909). Kim *et al.* adds the casein as a protein blocking layer for reducing non-specific interactions with the gold particles. Kim *et al.* teaches that since the gold particles are surrounded with protein molecules, *i.e.* immunoglobulin and casein as blocking agents for reducing non-specific interactions, a polymer shell is

rendered on the outside of the gold. (Kim *et al.* "Discussion", page 913, first paragraph). "This polymer shell may interfere with electron hopping, a dominant process of charge-transfer between the conducting mediators." (Kim *et al.* page 913, first paragraph of right column) Kim *et al.* further states that because "protein molecule could behave similarly to amorphous semiconductor, the shell thickness exceeding the distance required for efficient electron relay acts as a barrier against conduction." Kim *et al.* initially attempted to resolve the conduction barrier problem by using an external blocking molecular layer of polyethylene glycol instead of the casein. However, Kim *et al.* conclude:

> "Under the given conditions, the signal-to-noise ratio was enhanced by 30% as compared with the ionic protein coating, however the performance was still inferior to that of colorimetric detection. Therefore, it was concluded that the conductimetric analysis was relatively insensitive and was unsuitable for the system employing the conventional gold colloids as label."

(Kim *et al.*: first paragraph of Discussion, page 913).

Kim *et al.* then takes a different approach in an attempt to resolve the problem due to the electronic barrier surrounding the gold. After combining the antibody solution with the gold particles for conjugation, Kim *et al.*

"introduced, on the surface, polymeric conductor molecules that may bridge the neighboring particles or at least bring them closer to improve the charge-transfer state." Kim *et al.* uses polyaniline as the polymeric conductor molecule. "[P]olyaniline solutions diluted with PB in different concentrations (0.01-1 mg/ml) were added into the mixtures of gold and antibody and then reacted for 30 min." Kim *et al.* teaches that "[w]hen the polyaniline solution is added to the gold suspension, the molecules diffuse to the particle surface and subsequently adsorb to form an ordered layer on the residual sites after the antibody coating." (Kim *et al.*: page 913, right column, last paragraph). An illustration of the polyaniline polymer adsorbed on the surface of the gold particles is shown in the top frame of Figure 4 on page 912.

The mere fact that a reference can be modified by the Examiner does not render the resultant modification obvious unless the prior art also suggests the desirability of the modification. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). The teachings of Kim *et al.* would have suggested to those of ordinary skill in the art to keep the gold particles. In an attempt to resolve the electronic

barrier problem, Kim *et al.* did not suggest that it was desirable to remove the gold particles altogether, but rather introduce polymeric conductor molecules to improve the charge transfer *between* the gold particles. As taught by Kim *et al.* the "protrusion degree of the polymer strands, acting as a wire (*i.e.* molecular wires) for electrical connection, outside from the surface (refer to the top of Fig. 4) mainly depends on the polymer concentration applied and the molecular dimension." (Kim *et al.*: page 913, right column, last paragraph). The "extended filaments of the polymer in a plethora cross-linked the particles." (Kim *et al.*: page 913, right column, last paragraph).

Kim *et al.* makes it clear that the gold particles are important for the generation of a useful biosensor signal. One advantage of having the gold particles surfaces as taught Kim *et al.* is that "the presence of polymer strands on the surfaces may result in a high interfacial capacitance and, thus, a gain of conduction." (Kim *et al.*: first full paragraph, page 914). Kim *et al.* teaches that interfacial capacitance (not conductance) due to the presence of polymer strands on the surface of the gold particles is a major contributor to signal generation in a

low range of the gold concentration.

> "In a low range of gold concentration, the conductimetric signal increased in approximate proportion to the optical density, which could indicate the interfacial capacitance as a major contribution to the signal generation."

(Kim *et al.*: first full paragraph, page 914).

> "As another probable contribution, an increased fractal dimension by the presence of polymer strands on the surfaces may result in a high interfacial capacitance and, thus, a gain of conduction (Sergeyeva et al., 1996). From the dose-response curves in Fig. 6, the optical density value measured in the photometry would be proportional to the number of gold particles bound on the surfaces. In a low range of the gold concentration, the conductimetric signal increased in approximate proportion to the optical density, which could indicate the interfacial capacitance as a major contribution to the signal generation. To the contrary, as the optical density value approached the maximum, the conductivity abruptly increased in an exponential pattern (apparent in the bottom panel of Fig. 6). At this stage, the mean distance between gold colloids on the surfaces may be sufficiently close for electron hopping. <u>Therefore, the relative significance of the capacitance to the charge transfer on the signal generation in the proposed immunosensor seems to depend on the surface density of gold particles present in the circuit</u>." (Emphasis Added)

This knowledge would not lead a person of skill in the art to remove the gold particles and directly conjugate the antibody or other capture reagent directly to the polymeric conductor molecules. This teaching of an

interfacial capacitance of the polymer at low gold concentrations strongly suggests that the gold particles are the important component of the system, since the surface of the gold particles at high concentration provide electron hopping which accounts for the best results.

It is improper to modify a reference where the reference teaches away from the invention. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). Kim *et al.* teach the strategy of using the colloidal gold-antibody conjugates with the conducting polymer and not the direct labeling of the antibody with the conducting polymer by chemical reaction "because, in such a case, the protein molecule itself does not contain available sites for electron relay." (Kim *et al.*: Conclusions, page 914). Therefore, one skilled in the art reading Kim *et al.* would be directed away from eliminating the metal (gold) particles since Kim *et al.* teaches that direct labeling of the antibody with the polymer would not have the electron relay sites on the antibody protein molecule which are necessary for conduction.

One consideration which applies to obviousness rejections is that the references must be viewed without the

benefit of hindsight vision afforded by the claimed invention. "It is difficult but necessary that the decision maker forget what he or she has been taught . . . about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). The Kit et al. reference would not lead one skilled in the art to Applicants' claimed invention without hindsight. Reconsideration is requested.

B. The Examiner rejected Claims 3, 10, 22, 24 and 26 were rejected under 35 U.S.C. §103(a) as being unpatentable over Kim *et al.* (Biosensors & Bioelectronics 2000, 14: 907-915) in view of Roberts *et al.* (U.S. Patent No. 5,958,791).

Claims 3, 10, 22, 24 and 26 are patentable over Kim *et al.* for the reasons discussed above. Additionally, with regard to Claims 22, 24 and 26, Kim *et al.* fails to teach a multiple array of devices so that multiple analytes are detected simultaneously from the same sample. Roberts *et al.* teaches test devices including multiple sets of interdigitated electrode arrays for simultaneous multiple analyte detection and assay of a test sample for a plurality of analytes. However, Roberts *et al.* does not teach a *single* multiple array as taught by Applicants as illustrated in Figure 3. The simultaneous multiple analyte detection taught by Roberts *et al.* uses multiple sets of interdigitated electrode arrays in order to perform simultaneous multiple analyte detection to assay the test sample for a plurality of analytes. The liposome-enhanced immunoassay and test device taught by Roberts *et al.* would not suggest to a person of ordinary skill in the art the single multiple array as taught by Applicants, since the

nature of the immunoassay and test device taught by Roberts *et al.* requires separate competitive binding portions 104 and measurement portions 106. The test of Roberts *et al.* requires that a test mixture with the analyte of interest first passes through a competitive binding portion 104 having the binding material for the analyte before passing through a liposome lysing portion 106 where a liposome lysing agent releases the electroactive marker from the liposome. The electroactive marker is then carried by the migrating mixtures, via capillary action, into and through the electrochemical measurement portion to complete the electrical circuit (Roberts *et al.*: col. 15, line 53 through col. 16, line 5). A *single* multiple array as taught by Applicants and illustrated in Figure 3, wherein a plurality of analytes in a mixture can each be individually detected at one of the multiple regions 21A to 21D would not be suggested by the cited prior art references. In the embodiment illustrated in Figure 3, each one of the analytes bind to a specific capture reagent/antibody at one of the zones between the electrodes to generate a signal at one of the regions 21A-21E representative of that particular analyte. Each analyte will generate one of an array of

simultaneous voltage signals 33 which is proportional to the change of the resistance in that region. The immunoassay and test device taught by Roberts *et al.* does not show or suggest such an array, since specific binding must be completed *before* the test mixture flows between the electrodes in the measurement portion 106. If the adjacent electrodes are spaced too closely together in the immunoassay and test device taught by Roberts *et al.*, the electroactive marker can diffuse over to an adjacent region to generate a false signal in that region. Due to this possibility, the electrode arrays of Roberts *et al.*, unlike those arrays taught by Applicants, must be maintained at a large enough distance so that no electroactive markers can diffuse over the electrodes in an adjacent measurement portion 106. The design of the device taught by Applicants does not have this problem with cross-over signal. Since only the first capture reagent specific for the desired analyte is present between the electrodes only the desired complex of the analyte and second capture reagent bound to the electrically conductive polymer will be bound between the electrodes. Therefore any signal measured across the electrodes of any of the regions 21A to 21D is generated by

specific binding of the desired analyte to the region.

The combination of Kim et al. and Roberts et al. could not produce the claimed invention for the reasons previously discussed. Reversal of this rejection is requested.

C. Conclusion

The present Final Rejection is similar to the previous Final Rejection wherein Applicants filed a Brief Under 37 CFR §41.37. Basically, there was a similar rejection based upon Kim et al. which was withdrawn at that time. The present rejection merely attempts to incorrectly re-characterize the Conclusion of Kim et al.

As shown above, the device and system of the present invention is not obvious over the cited prior art references. Therefore, Claims 1-3, 7-10, 14-16, 18, 19, 21, 22, 24 and 26 are each patentable. Reversal of the Final Rejection is requested.

Respectfully,

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CLAIMS APPENDIX

1. A biosensor device which comprises:

a strip of a substrate having at least two zones wherein a

(1) first of the zones contains a first capture reagent bound to the substrate in a defined area between electrodes on different sides of the defined area for providing an electrical bias to the defined area; and

(2) a second of the zones containing a fluid transfer medium for supplying a fluid to the first zone, wherein the second zone comprises a second defined area containing a second capture reagent directly bound to an electrically conductive polymer formed by oxidative polymerization of monomers and the polymer has been mixed to react with the second capture reagent to form a conjugate, wherein there is an absence of electrically conductive particles, wherein when a fluid sample containing an analyte is bound by the second capture reagent to form a complex, the complex migrates to the first zone in the medium and the analyte is bound by the first capture reagent thereby altering a conductivity or resistance of the defined area in the first zone as measured between the electrodes to detect

the analyte.

2. The device of Claim 1 wherein the device further comprises a third zone adjacent to the first zone into which the fluid is absorbed after passing through the first defined area of the first zone.

3. The device of any one of Claims 1 or 2 wherein the first defined area has a dimension between the electrodes of 1.0 mm or less.

7. A system for detecting an analyte in a fluid sample which comprises:

(a) a biosensor device which comprises:

a strip of a substrate having at least two zones wherein a

(1) first of the zones contains a first capture reagent bound to the substrate in a defined area between electrodes on different sides of the defined area for providing an electrical bias to the defined area; and

(2) a second of the zones containing a fluid transfer medium for supplying a fluid to the first zone,

wherein the second zone comprises a second defined area containing a second capture reagent directly bound to an electrically conductive polymer formed by oxidative polymerization of monomers and the polymer has been mixed to react with the second capture reagent to form a conjugate, wherein there is an absence of electrically conductive particles, wherein when a fluid sample containing an analyte is bound by the second capture reagent to form a complex, the complex migrates to the first zone in the medium and the analyte is bound by the first capture reagent thereby altering a conductivity or resistance of the defined area in the first zone as measured between the electrodes;

(b) electrical means for supplying an electrical bias between the electrodes; and

(c) measuring means for determining a change in the conductivity or resistance of the first area before and after application of the sample in the second zone to detect the analyte.

8. A biosensor device which comprises:

a strip of a substrate having at least two zones wherein a

(1) first of the zones contains a first antibody bound to the substrate in a defined area between electrodes on different sides of the defined area for providing an electrical bias to the defined area; and

(2) a second of the zones containing a fluid transfer medium for supplying a fluid to the first zone, wherein the second zone comprises a second defined area containing a second antibody directly bound to an electrically conductive polymer formed by oxidative polymerization of monomers and the polymer has been mixed to react with the second capture reagent to form a conjugate, wherein there is an absence of electrically conductive particles, wherein when a fluid sample containing an antigen enters the second defined area of the second zone, the antigen is bound by the second antibody which is bound to the conductive polymer to form a complex, the complex migrates to the first zone in the medium and the antigen is bound by the first antibody thereby altering a conductivity or resistance of the defined area in the first zone as measured between the electrodes to detect the antigen.

9. The device of Claim 8 wherein the device further comprises a third zone adjacent to the first zone into which the fluid is absorbed after passing through the first defined area of the first zone.

10. The device of any one of Claims 8 or 9 wherein the first defined area has a dimension between the electrodes of 1.0 mm or less.

14. A system for detecting an antigen in a fluid sample which comprises:

(a) a biosensor device which comprises:

a strip of a substrate having at least two zones wherein a

(1) first of the zones contains a first antibody bound to the substrate in a defined area between electrodes on different sides of the defined area for providing an electrical bias to the defined area; and

(2) a second of the zones containing a fluid transfer medium for supplying a fluid to the first zone, wherein the second zone comprises a second defined area containing a second antibody directly bound to an

electrically conductive polymer formed by oxidative polymerization of monomers and the polymer has been mixed to react with the second capture reagent to form a conjugate, wherein there is an absence of electrically conductive particles, wherein when a fluid sample containing an antigen enters the second defined area of the second zone, the antigen is bound by the second antibody which is bound to the conductive polymer to form a complex, the complex migrates to the first zone in the medium and the antigen is bound by the first antibody thereby altering a conductivity or resistance of the defined area in the first zone as measured between the electrodes;

(b) electrical means for supplying an electrical bias between the electrodes; and

(c) measuring means for determining a change in the conductivity or resistance of the first area before and after application of the sample in the second zone to detect the antigen.

15. The system of Claim 14 wherein the device further comprises a third zone adjacent to the first zone into which the fluid is absorbed after passing through the first defined area of the first zone.

16. The device of Claim 1 or 2 wherein a third zone adjacent to the second zone is provided for applying the fluid sample containing the analyte prior to being introduced into the second zone.

18. The system of Claim 7 or 8 wherein a pad adjacent to the second zone is provided for applying the fluid sample containing the analyte prior to being introduced into the second zone.

19. The device of Claim 8 or 9 wherein a pad adjacent to the second zone is provided for applying the fluid sample containing the analyte prior to being introduced into the second zone.

21. The system of Claim 14 or 15 wherein a pad adjacent to the second zone is provided for applying the fluid sample containing the analyte prior to being introduced into the second zone.

22. The device of Claim 1 or 2, wherein the biosensor device is a multi-array device comprising:

a plurality of first zones on the single strip of substrate, each of the first zones having a first capture reagent with a different specificity bound to the single strip of substrate between electrodes to immobilize one of multiple analytes on the single strip of substrate so that each of the multiple analytes can be detected simultaneously from the same sample on the single strip of substrate of the multi-array biosensor device.

24. The device of Claim 8 or 9, wherein the biosensor device is a multi-array device comprising:

a plurality of first zones on the single strip of substrate, each of the first zones having a first capture reagent with a different specificity bound to the single strip of substrate between electrodes to immobilize one of

multiple analytes on the single strip of substrate so that each of the multiple analytes are detected simultaneously from the same sample on the single strip of substrate of the multi-array biosensor device.

26. The system of Claim 14 or 15, wherein the biosensor device is a multi-array device comprising:

a plurality of first zones on the single strip of substrate, each of the first zones having a first capture reagent with a different specificity bound to the single strip of substrate between electrodes to immobilize one of multiple analytes on the single strip of substrate so that each of the multiple analytes can be detected simultaneously from the sample on the single strip of substrate of the multi-array biosensor device by providing a constant current and measuring generated voltage signals proportional to resistances across each of the first zones.

EVIDENCE APPENDIX

Attached Declaration Under 37 CFR 1.132

RELATED PROCEEDINGS APPENDIX

(None.)

Attachment

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 10/074,499	Confirmation No. 4246
Applicants	: Evangelyn C. Alocilja and Zarini Muhammad-Tahir	
Filed	: February 13, 2002	
Title	: CONDUCTIMETRIC BIOSENSOR DEVICE, METHOD AND SYSTEM	
TC/A.U.	: 1641	
Examiner	: Leon Y. Lum	
Docket No.	: MSU 4.1-587	
Customer No.	: 21036	

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

Dear Sir:

Evangelyn C. Alocilja states as follows:

(1.) That she is an inventor of the invention in the above entitled application.

(2.) That she is an Associate Professor of Biosystems Engineering at Michigan State University, East Lansing, Michigan 48824.

(3.) That the conductive polyaniline polymers synthesized by oxidative polymerization of aniline monomers, as described in Example 1 of the above entitled application, form polymer strands.

(4.) That these conductive polyaniline polymers strands of Example 1 are reacted directly with the antibodies, without using glutaraldehyde.

(5.) That these conductive polyaniline polymers synthesized by oxidative polymerization of aniline monomers are formed in the absence of any conductive particles.

MSU 4.1-587
Appl. No. 10/074,499
November 10, 2006

(6.) That the undersigned declares further that all statements made herein of her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

ECAlocilja
Evangelyn C. Alocilja

Date: 11/10/06